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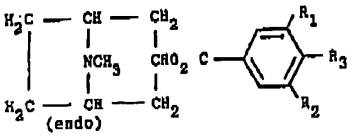
(54) **Treatment of migraine with tropyl benzoate derivatives**

(57) Migraine is treated with a tropyl benzoate derivative of the following general Formula I:—



wherein:—

R_1 represents C_1—C_4 alkyl, C_1—C_4 alkoxy; or halogen;

R_2 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen; and

R_3 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy, or halogen provided that R_3 is hydrogen when R_2 is hydrogen.

Some of the tropyl benzoate derivatives of Formula I are novel compounds.

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The chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

Treatment of migraine with tropyl benzoate derivatives

FIELD OF THE INVENTION

The invention relates to the treatment of migraine with certain tropyl benzoate derivatives and provides pharmaceutical compositions comprising said compounds and methods of treating migraine using said compounds. Further, the invention also provides said compounds for use in treating migraine and, when said compounds are novel, it provides said novel compounds *per se*.

BACKGROUND OF THE INVENTION

Acute attacks of migraine are usually treated with a peripheral vascoconstrictor, such as ergotamine, which may be co-administered with caffeine, and dihydroergotamine; an antipyretic analgesic, such as acetylsalicyclic acid or p-acetylaminophenol; and/or an anti-emetic such as cyclizine, metoclopramide and thiethylperazine. It has also been reported (J.B. Hughes; Med. J. Aust. 2, No. 17, 580, 1977) that immediate relief of acute migraine attack can be obtained by slow intravenous injection of metoclopramide (10 mg).

It is believed that 5-hydroxytryptamine (5—HT) is the naturally occuring substance most likely to play a role in the pathophysiology of migraine. Increased amounts of the 5—HT and its metabolite 5-hydroxyindole-acetic acid are excreted in the urine during most attacks. Further, plasma and platelet 5—HT concentrations fall rapidly at the onset of an attack and remain low whilst the headache persists. Moreover, attacks of migraine have been clearly associated with periods of thrombocytopaenia in certain patients. It has been proposed that compounds which block the activity of 5—HT would be of use in the treatment of migraine (J.R. Fozard, International Headache Congress 1980) reported in Advances in Neurology, Vol 33, Raven Press, New York 1982).

The known migraine prophylactic drugs methysergide, propanolol, amitriptyline, and chlorpromazine have widely different pharmacological activities but are all 5—HT D-receptor antagonists at the doses used clinically for the treatment of migraine. Metoclopramide is a potent 5—HT M-receptor antagonist and it has been proposed (J.R. Fozard *supra*) that blockade of the M-receptor present on afferent sensory neurones affords symptomatic relief in an acute migraine attack.

It is an object of the present invention to provide compounds which are more potent and selective 5—HT M-receptor antagonists than metoclopramide and hence indicated for use in the treatment of migraine.

The potency as 5—HT M-receptor antagonists of (—) cocaine and some related compounds has been reported (J.R. Fozard *et al*, Eur. J. Pharmacol., 59(1979), 195—210) but, with the exceptions of nor(—)cocaine and benzoyltropine, none are as potent as metoclopramide. The pA_2 values reported for nor(—)cocaine and benzoyltropine are 7.7 and 7.12 respectively whilst the pA_2 5—HT value determined for metoclopramide by the same procedure is 7.2 (J.R. Fozard *et al*. Eur. J. Pharmacol., 49(1978), 109—112).

Surprisingly, it has been found that substitution of benzoyltropine by alkyl, alkoxy or halogen in the 3, 3 and 5, or 3, 4 and 5 positions of the benzene ring substantially enhances its potency as a 5—HT M-receptor antagonist.

The tropyl benzoate derivatives of Formula I set forth in the following Table I are known compounds.

TABLE I

KNOWN TROPYLBENZOATES OF FORMULA I

R_1	R_2	R_3	*Reference*
OCH_3	H	H	e.g.C.A. *59*, 5665
OCH_3	OCH_3	OCH_3	
OCH_3	OCH_3	OC_4H_9	C.A. *67*, 53953
Cl	H	H	e.g.C.A. *78*, 119197
Cl	Cl	H.	

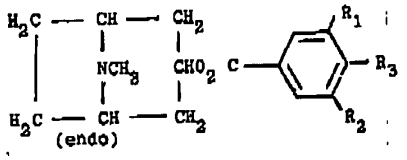
Some of the said known tropyl benzoate derivatives and certain known positional isomers thereofs have been reported to have pharmacological activity, specifically local anesthetic, central nervous system stimulant, cholinolytic and/or spasmolytic activity. However no pharmacological activity indicating use in the treatment f migraine has been reported.

The compounds of Formula I can be effectively administered in the treatment of migraine at dose levels well below those at which pharmagological activity has previously been reported for any of the

said known compounds or their known isomers.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there are provided for use in the treatment of migraine and other vascular headaches a tropyl benzoate derivative of the following general Formula I:—



wherein:—

R_1 represents C_1—C_4 alkyl, C_1—C_4 alkoxy; or halogen;

R_2 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen; and

R_3 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy, or halogen provided that R_2 is hydrogen when R_2 is hydrogen, or a pharmaceutically acceptable salt thereof.

According to a second aspect of the invention there are provided pharmaceutical compositions in unit dose form of the effective relief of migraine comprising a compound of general Formula I in admixture or otherwise associated with a pharmaceutically acceptable diluent or carrier and containing 0.5 to 100 mg per unit dose. Usually, said compositions will contain 1 to 50 mg, especially 3 to 30 mg, per unit dose.

According to a third aspect of the invention, there are provided *per se* compounds of Formula I excluding those listed in Table I.

According to a fourth aspect of the invention, there is provided a method of treating migraine which comprises administering to a patient suffering migraine, an effective migraine relieving amount of a compound of Formula I. Said amount usually will be in the range 0.01 mg/kg to 10 mg/kg, especially 0.03 mg/kg to 3.0 mg/kg. It is also contemplated that the compounds of Formula I can be used in the phrophylaxis of migraine by administering to a patient at risk of migraine an effective migraine-prophylatic amount of the compound.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of general Formula I have the benzoyloxy moiety substituted in that R_1 represents C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen; R_2 can represent C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen instead of hydrogen; and R_3 is hydrogen except when R_2 is other than hydrogen, in which case R_3 can represent C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen instead of hydrogen.

Examples of C_1—C_4 alkyl groups which can be represented by R_2, R_3 and R_4 are methyl, ethyl, *n*-propyl, *N*-butoxy and *iso*-propyl with methyl and ethyl being preferred.

Examples of C_1—C_4 alkoxy groups which can be represented by R_2, R_3 and R_4 are methoxy, ethoxy, *n*-propoxy, *n*-butoxy and *iso*-propoxy, with ethoxy and especially, methoxy being preferred.

The halogens which can be represented by R_2, R_3 and R_4 are bromine, chlorine, fluorine and iodine with bromine, fluorine and, especially, chlorine being preferred.

One preferred class of compounds are those of Formula I in which R_1 represents methyl, methoxy or chlorine, R_2 represents hydrogen, and R_3 represents hydrogen.

Another preferred class of compounds are those of Formula I in which R_1 and R_2 are the same and each represents methyl, methoxy or chlorine, and R_3 represents hydrogen.

Yet another preferred class of compounds are those of Formula I in which R_1, R_2 and R_3 are all the same and each represents methyl, methoxy or chlorine.

In one presently particularly preferred embodiment of the invention, the compounds are those of Formula I in which (a) R_1 represents methoxy and R_2 and R_3 represent hydrogen, (b) R_1 and R_2 both represents methoxy and R_3 represents hydrogen, or (c) R_1, R_2 and R_3 erach represent methoxy. Said compounds are:—

tropyl-3-methoxybenzoate

tropyl-3,5-dimethoxybenzoate, and

tropyl-3,4,5-trimethoxybenzoate

The di- and tri-methoxy compounds are preferred over the monomethoxy compound.

In another presently particularly preferred embodiment of the invention, the compounds are those of Formula I in which (a) R_1 represents chlorine and R_2 and R_3 represent hydrogen, (b) R_1 and R_2 both represent chlorine and R_3 represents hydrogen, or (c) R_1, R_2 and R_3 each represent chlorine. Said compounds are:—

tropyl-3-chlorobenzoate

tropyl-3,5-dichlorobenzoate

tropyl-3,4,5-trichlorobenzoate

The dichloro compound is presently preferred to the mono-or tri-chloro compounds.

In addition to the preferred methoxy and chloro compounds specified above, the following are illustrative compounds of Formula I:—

tropyl 3,5-dibromobenzoate;
tropyl 3,5-diiodobenzoate;
tropyl 3,5-difluorobenzoate;
tropyl 3,5-diethoxybenzoate;
tropyl 3-methoxy-5-chlorobenzoate;
tropyl 3-methyl-benzoate;
tropyl 3,5-dimethylbenzoate;
tropyl 3,4,5-trimethylbenzoate;
tropyl 3,5-diethylbenzoate;
tropyl 3,5-di *n*-butoxybenzoate;

The compounds of Formula I block the M-receptors for 5-hydroxytryptamine (5—HT) on afferent sensory neurones, certain of which subserve the transmission of pain. As explained above, the blocking of such M-receptors is believed to be a mechanism by which the symptoms of migraine can be relieved. Accordingly, the compounds of Formula I are useful in the treatment of migraine when administered in amounts sufficient to effectively block the said M-receptors.

The activity of the compounds against 5—HT can be assessed by determining their pA_2 values in the isolated rabbit heart as described by Fozard *et al* Europ. J. Pharmacol. *59*, 195—210 (1979). In the method described the molar concentration of antagonist which reduces the effects of twice the ED50 of 5—HT to that of the ED50 in the absence of antagonist is determined. The pA_2 value is the negative logarithm of said molar concentrations. In general terms, the higher the pA_2 value the more potent is the compound.

The pA_2 values of some representative compounds of Formula I are given in the following Table II:—

TABLE II

Compound	*pA_2 5—HT*
tropyl 3- methylbenzoate	8.2
tropyl 3,5-dimethoxybenzoate	8.4
tropyl 3,4,5-trimethoxybenaoate	8.5
tropyl 3-chlorobenzoate	8.6
tropyl 3,5-dimethylbenzoate	9.0
tropyl 3,5-dichlorobenzoate	9.3

The pA_2 values of some closely structurally related compounds to those of the invention are given in the following Table III for comparative purposes.

TABLE III

Compound	*pA_2 5—HT*
tropyl 4-chlorobenzoate	7.0
tropyl 3,4-dimethoxybenzoate	7.2
tropyl benzoate	7.2
tropyl 4-methylbenzoate	7.8
nortropyl 3,5-dichlorobenzoate	7.8

It will be noted from Tables II and III that the compounds of Formula I show in this test a potency as 5—HT M-receptor antagonists at least an order greater than that of tropylbenzoate.

The activity of the compounds against 5—HT can be assessed *in vivo* by measurement of the effect of the compound on the V n Bezold-Jarixch Reflex Induced by 5—HT injected intravenously into the rat (see Paintal A.S., Physiol. R v. *53* 159—227, 1973). The transient cardiac slowing arises from an increased efferent vagus activity arising from stimulation by 5—HT of sensory afferent fibres in and

around the heart (see Example 3).

The compounds of Formula I are highly selective in their action against 5—HT M—receptor. Their potency against other 5—HT receptors and other spasmogens, in particular oxytocin, acetylcholine, histamine and calcium, appears to be at least two orders lower than that against 5—HT M-receptors (see Example 4). Accordingly, their use in the treatment of migraine should be without any side effects.

The compounds of Formula I can be administered in various manners to achieve the desired effect. The compounds can be administered alone or in the form of pharmaceutical preparations to the patient being treated either orally or parenterally, for example, subcutaneously or intravenously. The amount of compound administered will vary and can be any effective migraine-relieving amount. Depending upon the patient and the mode of administration, the quantity of compound administered may vary over a wide range to provide from about 0.01 mg/kg to about 10 mg/kg, usually 0.03 to 3.0 mg/kg, of body weight of the patient per dose. Unit doses of these compounds can contain, for example, from about 0.5 mg to 100 mg, usually 1 to 50 mg and preferably 3 to 30 mg, of the compound and may be administered, for example, from 1 to 4 times daily.

It will be appreciated that the dosage levels referred to above are substantially less than those which would be required for medical treatment based on any known pharmacological activity of any of the known compounds of Formula I. In the particular case of, for example, tropine-3,5-dichlorobenzoate, *In vitro* data (see Table VI) indicate that the dose levels for treating migraine are between 4,500 and at 62,000 times less than that required to produce spasmolytic effects.

The term "unit dosage form" is used herein to mean a single or multiple dose form containing a quantity of the active ingredient in admixture with or otherwise in association with the diluent or carrier, said quantity being such that one or more predetermined units are normally required for a single therapeutic administration. In the case of multiple dose forms such as liquids or scored tablets, said predetermined unit will be one fraction, such as a 5 ml (teaspoon) quantity of a liquid or a half or quarter of a scored tablet, of the multiple dose form.

In the composition aspect of the invention there are provided pharmaceutical formulations in which form the active compounds of the invention will normally be utilized. Such formulations are prepared in a manner well known *per se* in the pharmaceutical art and usually comprise at least one active compound of the invention in admixture or otherwise in association with a pharmaceutically acceptable carrier or diluent therefor. For making those formulations the active ingredient will usually be mixed with a carrier, or diluted by a diluent, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other container. A carrier or diluent may be solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active ingredient. Suitable carriers or diluents are well known *per se*.

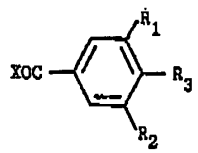
The formulations of the invention may be adapted for enteral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solutions, suspensions or the like.

In the specific examples included hereinbelow illustrative examples of suitable pharmaceutical formulations are described.

The tropyl benzoate derivatives of Formula I can be used in migraine therapy with antimigraine drugs having different modes of action. Such drugs include those used prophylactically, such as barbiturates, diazepam, chlorpromazine, amitriptyline, propanolol, methysergide, pizotifen, cyproheptadine, dihydroergotamine, and clonidine, and those used in the acute attack, such as vascoconstrictor agents, e.g. ergotamine and dihydroergotamine, analgaesic/anti-inflammatory agents, e.g. aspirin, paracetamol and indomethacin, or anti-nauseants, e.g. cyclizine, metoclopramide, and triethylperazine (see Fozard, M.R. J. Pharm. Pharmacol. 27, 297—321 (1975); Saper, J.R., J. Amer. Med. Assoc. *239*, 480—484 (1978); Fozard, J.R., supra.) As an example, compounds of general Formula 1 would be beneficial in combination with aspirin 300—1200 mg or methysergide, 2—6 mg given daily.

As mentioned above, certain of the compounds of Formula I are known compounds and hence their preparation or, in the case of naturally occurring compounds, their isolation is described in the literature.

The compounds of general Formula I can be prepared in manner known *per se* from tropine and an acid halide of the following general Formula IV:—



Formula IV

wherein:—

R_1, R_2 and R_3 are as defined in connection with Formula I, and

X represents halogen, especially chlorine.

The reaction can be carried out in the absence of a solvent by heating at, for example, a temperature in the range 140° to 160°C the acid halide with a hydrohalide salt of tropine whilst stirring. Hydrogen halide is evolved and the mixture first becomes liquid but subsequently becomes solid. Heating is continued for about 15 mins after solidification and the mixture is then cooled and added to water. The product is the hydrohalide of the compound of Formula I and the free base can be obtained by addition of aqueous base, such as sodium or portassium carbonate, which does not hydrolyse the ester, to render the aqueous product solution alkaline and subsequent extraction of the free base with a suitable organic solvent such as, for example, diethyl ether, ethylacetate and methylene chloride. The organic solution is subsequently evaporated and the residue recrystallized from, for example, aqueous methanol.

As mentioned previously, the compounds of Formula I can be used in the form of their pharmaceutically acceptable acid addition salts.

The pharmaceutically acceptable acid addition salts can be non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulfuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, malic, tartaric, citric, salicyclic, *o*-acetyloxybenzoic, nicotinic or isonicotinic, or organic sulphonic acids, for example methane sulphonic, ethane sulphonic, 2-hydroxyethane sulphonic, toluene-*p*-sulphonç, or naphthalene-2-sulphonic acids.

Apart from pharmaceutically acceptable acid addition salts, other acid addition salts, such as for example, those with picric or oxalic acid, may be serve as intermediates in the purification of the compounds or in the preparation of other, for example, pharmaceutically acceptable, acid addition salts, or are useful for identification or characterisation of the bases.

An acid addition salt may be converted into the free compound according to known methods, for example, by treating it with a base, such as with a metal hydroxide or alkoxide, for example an alkali or alkaline earth metal hydroxide, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium hydroxide; with a metal carbonate, such as an alkali metal or an alkaline earth metal carbonate or hydrogen carbonate, for example, sodium, potassium or calcium carbonate or hydrogen carbonate; with trialkylamine; or with an anion exchange resin.

An acid addition salt may also be converted into another acid addition salt according to known methods; for example, a salt with an inorganic acid may be treated with a metal salt, for example a sodium, barium or silver salt, or an acid in a suitable diluent, in which a resulting inorganic salt is insoluble and is thus removed from the reaction medium. Acid addition salt may also be converted into another acid addition salt by treatment with an anion exchange preparation.

The invention is illustrated in the following non-limiting Examples.

EXAMPLE 1

TROPYL 3,5-DICHLOROBENZOATE

(FORMULA I, R_1=R_2=Cl, R_3=H)

Tropine (34.24 g) is treated with anhydrous diethyl ether and ethereal hydrogen chloride and the precipitated hydrochloride is isolated by evaporation of the solvent. 3,5 Dichlorobenzoylchloride (51.7 g) is added and the mixture stirred at 140°C for 15 mins during which time the mixture liquefies, evolves hydrogen chloride gas and resolidifies. After heating for a further 15 mins the cooled solid is dissolved in water, an excess of an aqueous solution of potassium carbonate is added, and the base is extracted with ethyl acetate. Evaporation of the dried ethyl acetate solution gives a solid which is recrystallised from aqueous methanol to give tropyl 3,5 dichlorobenzoate m.p. 95°C (51.8 g).

$C_{15}H_{17}NO_2Cl_2$

Calculated	C, 57.33	H, 5.46	N, 4.46%
Found	C, 57.55	H, 5.53	N, 4.47%

The following compounds are prepared by the same method.

tropyl 3,5 dimethoxybenzoate m.p. 200°C

tropyl 3-chlorobenzoate hydrochloride m.p. 235—6°C

tropyl 3,4,5 trimethoxybenzoate m.p. 118°C

EXAMPLE 2

TROPYL 3,5-DIMETHYLBENZOATE HYDROCHLORIDE

(FORMULA I, R_1=R_2=CH_3, R_3=H)

A stirred mixture of tropine hydrochloride (5.27 g) and 3,5-dimethyl benzoyl chloride (5 g) is heated at 130—140° for 30 minutes during which time the mixture liquifies, evolves hydrogen chloride gas and resolidifies. A solution of the cooled solid in water is basified with a solution of potassium carbonate and the base extracted with ethyl acetate. The ethyl acetate solution is washed several times with water, dried over magnesium sulphate, and evaporated to give the free base which is converted t the hydrochloride by the addition of ethereal hydrogen chloride. Recrystallization of the precipitated

solid from ethanol gives crystal of tropyl 3,5-dimethylbenzoate hydrochloride (5.4 g) mp 260°.
$C_{17}H_{24}NO_2Cl$

Calculated	C 66.88	H 7.75	N 4.52%
Found	C 65.92	H 7.67	N 4.34%

EXAMPLE 3

Antagonism of the von Bezold-Jarisch reflex evoked by 5—HT in the anaesthetised rat was measured for tropyl-3,5-dimethoxybenzoate (A) tropyl-3,5-dimethylbenzoate (B) and tropyl-3,5-dichlorobenzoate (C) using the following method.

Male Sprague-Dawley rats weighing 250—300 g are anaesthetized with urethane, 1.25 g/kg injected intraperitoneally and set up for recording blood pressure and heart rate as described in Fozard JR *et al.*, J. Cardiovasc. Pharmacol. 2, 229—245 (1980). a submaximal dose of 5—HT (2 μg/kg) is given repeatedly into the cannulated jugular vein and changes in heart rate quantified. Antagonists are given intravenously and the doses required to just inhibit the response to 5—HT (threshold dose) or to inhibit the response to 5—HT by 50% (ED50) are determined.

The results obtained are set forth in Table IV below in which the compounds are identified by the reference letters used above.

TABLE IV

VON BEZOLD-JARISCH REFLEX ANTAGONISM

COMPOUND	THRESHOLD DOSE (μg/kg)	ED50 (μg/kg)
A	6.96±0.90	13.7±1.20
B	3.57±0.33	6.07±0.72
C	7.72±0.63	22.0±3.2

In a comparative test metoclopramide gave a threshold dose of 233.4±66.3 μg/kg and an ED50 of 408.4±80.9 μg/kg.

This comparative test shows that compounds A, B and C are many times more potent than metoclopramide in this particular test indicating a corresponding reduction in dosage levels in the treatment of migraine.

Compounds A, B and C are also relatively non-toxic as shown by their respectice LD50 values in the mouse and rat (see Table V).

TABLE V

LD50 IN THE MOUSE AND RAT (mg/kg)

ROUTE	MOUSE			RAT		
	A	B	C	A	B	C
i.p.	28	32	47	NT	NT	NT
s.c.	17	NT	NT	NT	NT	NT
i.v.	28	24	17	13	14	9
oral	160	90	116	NT	NT	NT

(NT = not tested)

EXAMPLE 4

SELECTIVITY OF ACTION

A selection of classical *in vitro* pharmacological test preparations (rat uterus; rat fundus; guinea-pig ileum; guinea-pig taenia caeci) were set up according to well-established procedures (see "Pharmacological experiments on isolated preparations" Steff of the Department of Pharmacology,

University of Edinburgh, Livingstone, Edinburgh 1970). Various spasmogens were used to elicit contraction of these tissues through mechanisms other than the 5—HT "M" receptor. The concentrations of tropyl-3,5-dimethoxybenzoate (A) tropyl-3,5-dimethylbenzoate (B) and tropyl-3,5-dichlorobenzoate (C) which reduced the effects of a submaximal dose of agonist by 50% were determed (IC50). The results are set forth in Table VI below in which the compounds are identified by the reference letters used above.

From Table VI it is clear that A, B and C were at least 700 times and in several instances greater than 50,000 times more potent as blockers of the 5—HT M receptor than of responses elicited through other means.

TABLE VI

(CONCENTRATION IN NM TO INHIBIT STANDARD RESPONSE TO STIMULTANTS BY 50%

AGONIST	RABBIT HEART			RAT UTERUS		RAT FUNDUS		GUINEA-PIG ILEUM			GUINEA-PIG TAENIA CAECI*		
	A	B	C	A	B	A	B	A	B	C	A	B	C
5HT	9.4	1.03	0.82	>52480	26440	40016	>50880						
OXYTOCIN				>52480	>50880								
ACETYLCHOLINE						13120	12402	9565	9590**	8055			
HISTAMINE								6813	NT	3676			
CALCIUM											36080	34230	28620

* In potassium-depolarised Tyrode solution
** Carbachol agonist instead of Acetylcholine
NT Not Tested

EXAMPLE 5

PILOT STUDY OF TOLERANCE TO INTRAVENOUS TROPYL-3,5-DICHLOROBENZOATE IN PATIENTS WITH MIGRAINE OR CLUSTER HEADACHES

This study was designed to evaluate tolerance and, if possible, efficacy of intravenous tropyl-3,5-dichlorobenzoate in patients with migraine or cluster headaches.

Eight patients (4 males), aged 27—47 with known headache disorders of 5—27 years duration (see Table VI) took part in the study but Patient Nos. 2 and 4 had cluster not migraine headaches and the cause of headaches in Patient No. 6 was unknown.

Tropyl-3,5-dichlorobenzoate was provided as a sterile solution, 1 mg/ml; the desired dose to be diluted in 10 ml normal saline for intravenous infusion over a 2 minute period. No other therapy was taken for at least 24 hours before treatment or during the course of therapy.

The initial dose of 1 mg, when shown to be well tolerated, was increased gradually in subsequent patients, (Table VII). Doses as high as 14 mg/day and 9 mg single dose were administered without any signs of intolerance. Cumulative doses as high as 177 mg over 18 days were also well tolerated.

In 2 of the 3 patients treated with repeated doses of tropyl-3,5-dichlorobenzoate (patients 6 and 8), a marked diminution of headache and associated symptoms occurred. Thus, Patient No. 6, refractory to standard migraine therapies, had a slight reduction in her bilateral headache with 3 mg single doses and a further amelioration with 4 mg bid. This reduction in headache intensity lasted over a $2\frac{1}{2}$ week period. Patient No. 8, an abuser of analgesics with daily bilateral headaches accompanied by nausea, vomiting, vertigo and photophobia, had a decrease in all symptoms with the first dose of 3 mg. This amelioration continued with subsequent increases in doses, except for a single episode of symptom return on first day of 9 mg. Within 6—7 days of stopping therapy, headache returned to pre-treatment intensity.

It can be seen from Table VII that single intravenous doses of tropyl-3,5-dichlorobenzoate up to 9 mg or repeated doses up to 7 mg bid were well tolerated in patients with headaches. In some patients treated with doses of 3 mg or greater, pain intensity and associated symtoms were ameliorated.

TABLE VI

PATIENT CHARACTERISTICS

Patient	Sex	Age	Weight	Type of Headache	History of Headache	Usual Freq.	Usual Duration
1	M	45	85	Chronic with exacerbations	19 years	2—3/wk	18—24 hours
2	M	27	70	Cluster	5 years	daily	30—45 min
3	F	31	67.4	Continuous with exacerbations	10 years	daily	continuous
4	M	47	66	Cluster	11 years	2—3/day	1—2 hours
5	M	43	84.7	Chronic with daily crises, "Horton-like"	20 years	daily	3—4 hours
6	F	45	74	?	27 years	daily	?
7	F	34	53	Continuous with exacerbations, and extracranial pain	11 years	3—4/week	3—5 hours
8	F	36	51.2	Chronic with daily exacerbations	7 years	daily	4—6 hours

TABLE VII

TREATMENT AND RESPONSE

Patient	Posology (intravenous)	Response	Tolerance
1	1 mg, then 1 hour later 2 mg	no effect on headache or nausea	good
2	1 mg	no effect	good
3	3 mg	no effect	good
4	3 mg	no effect	good
5	5 mg	no effect	good
6	3 mg single doses x 3 days, then 4 mg bid x 2 days, then 5 mg bid x 2 days then 6 mg bid x 11 days.	reduction of pain intensity by 70—80% within within 30 minutes after 4 mg dose and lasting 4—8 hours; no greater effect with increased doses.	good
7	3 mg x 1 day, then 5 mg x 2 days then 7 mg x 1 day.	no effect	good
8	3 mg x 2 days, then 6 mg x 1 day, 7 mg x 2 days and 9 mg x 1 day.	reduction of pain by about 30% with 3 mg, and maintained during increasing doses except for single episode of pain, nausea, vomiting and photophobia on first day of 9 mg.	good

In the following Examples relating to pharmaceutical compositions, the term "active compound" is used to indicate the compound tropyl-3,5-dichlorobenzoate. This compound may be replaced in these compositions by any other compound of Formula I, for example by tropyl-3,5-dimethoxybenzoate. Adjustments in the amount of medicament may be necessary or desirable depending upon the degree of activity of the medicament as is well known in the art.

EXAMPLE 6

An illustrative composition for hard gelatin capsules is as follows:—

(a) active compound	5 mg
(b) talc	5 mg
(c) lactose	90 mg

The formulation is prepared by passing the dry powders of (a) and (b) through a fine mesh screen and mixing them well. The powder is then filled into hard gelatin capsules at a net fill of 100 mg per capsule.

EXAMPLE 7

An illustrative composition for tablets is as follows:—

(a) active compound	5 mg
(b) starch	43 mg
(c) lactose	50 mg
(d) magnesium stearate	2 mg

The granulation obtained upon mixing the lactose with the compound (a) and part of the starch and granulated with starch paste is dried, screened, and mixed with the magnesium stearate. The mixture is compressed into tables weighing 100 mg each.

EXAMPLE 8

An illustrate composition for an injectable suspension is the following 1 ml ampul for an intramuscular injection:—

	Weight per cent
(a) active compound	0.01
(b) polyvinylpyrrolidone	0.5
(c) lecithin	0.25
(d) water for injection to make	100.00

The material (a)—(d) are mixed, homogenized, and filled into 1 ml ampuls which are sealed and autoclaved 20 minutes at 121°C. Each ampul contains 1.0 mg per ml of compound (a).

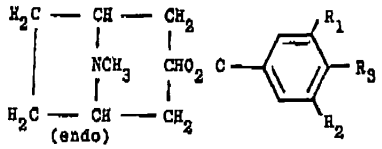
EXAMPLE 9

	mg/suppository
Active Compound	5
Oil of Theobroma (cocoa butter)	995

The medicament is powdered and passed through a B.S. No. 100 Sieve and triturated with molten oil of Theobroma at 45°C to form a smooth suspension. The mixture is well stirred and poured into moulds each of nominal 1G capacity, to produced suppositories.

CLAIMS

1. A pharmaceutical composition in unit dose form for the treatment of migraine comprising, in admixture or otherwise associated with a pharmaceutically acceptable diluent or carrier, an amount of 0.5 to 100 mg per unit dose of a tropyl benzoate derivative of the following general Formula I:—



wherein:—

R_1 represents C_1—C_4 alkyl, C_1—C_4 alkoxy; or halogen;

R_2 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen; and

R_3 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy, or halogen provided that R_3 is hydrogen when R_2 is hydrogen; or a pharmaceutically acceptable salt thereof.

2. A composition as claimed in Claim 1 containing 1 to 50 mg of said compound per unit dose.

3. A composition as claimed in Claim 2 containing 3 to 30 mg of said compound per unit dose.

4. A composition as claimed in any one of the preceding Claims wherein R_1 represents methyl, methoxy or chlorine, R_2 represents hydrogen, and R_3 represents hydrogen.

5. a composition as claimed in any one of claims 1 to 3 wherein R_1 and R_2 are the same and each represents methyl, methoxy or chlorine, and R_3 represents hydrogen.

6. A composition as claimed in any one of Claims 1 to 3 wherein R_1, R_2 and R_3 are all the same and each represents methyl, methoxy or chlorine.

7. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3-methoxybenzoate or a pharmaceutically acceptable salt thereof.

8. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3,5-dimethoxybenzoate or a pharmaceutically acceptable salt thereof.

9. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3,4,5-trimethoxybenzoate or a pharmaceutically acceptable salt thereof.

10. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3-chlorobenzoate or a pharmaceutically acceptable salt thereof.

11. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3,4-dichlorobenzoate or a pharmaceutically acceptable salt thereof.

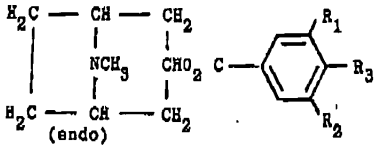
12. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3,4,5-trichlorobenzoate or a pharmaceutically acceptable salt thereof.

13. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3-methylbenzoate or a pharmaceutically acceptable salt thereof.

14. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3,5-dimethylbenzoate or a pharmaceutically acceptable salt thereof.

15. A composition as claimed in any one of Claims 1 to 3 wherein the tropylbenzoate derivative is tropyl-3,4,5-trimethylbenzoate or a pharmaceutically acceptable salt thereof.

16. A tropyl benzoate derivative of the following general Formula I:—



wherein:—

R_1 represents C_1—C_4 alkyl, C_1—C_4 alkoxy; or halogen;

R_2 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen; and

R_3 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy, or halogen provided that R_3 is hydrogen when R_2 is hydrogen

excluding those in which R_1, R_2 and R_3 are in a combination specified in Table I hereinbefore, or a pharmaceutically acceptable salt thereof.

17. Tropyl-3,5-dimethoxybenzoate or a pharmaceutically acceptable salt thereof.

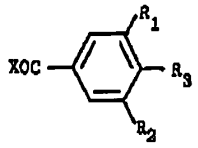
18. Tropyl-3-methylbenzoate or a pharmaceutically acceptable salt thereof.

19. Tropyl-3,5-dimethylbenzoate or a pharmaceutically acceptable salt thereof.

20. Tropyl-3,4,5-trimethylbenzoate or a pharmaceutically acceptable salt thereof.

21. Tropyl-3,4,5-trichlorobenzoate or a pharmaceutically acceptable salt thereof.

22. A process for preparing a compound as claimed in Claim 16 which comprises the reaction in manner known *per se* of tropine and the corresponding acid halide of the following general Formula IV

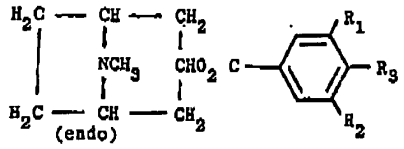


Formula IV

wherein R_1, R_2 and R_3 are as defined in Claim 16 and X represents halogen.

23. A process as claimed in Claim 22 wherein a hydrohalide salt of tropine is heated with the acid halide in the absence of a solvent.

24. A tropyl benzoate derivative of the following general Formula I:—



wherein:—

R_1 represents C_1—C_4 alkyl, C_1—C_4 alkoxy; or halogen,

R_2 represents hydrogen, C_1—C_4, alkyl, C_1—C_4 alkoxy or halogen; and

R_3 represents hydrogen, C_1—C_4 alkyl, C_1—C_4 alkoxy, or halogen provided that R_3 is hydrogen when R_2 is hydrogen

excluding those in which R_1, R_2 and R_3 are in a combination specified in Table I hereinbefore, and pharmaceutically acceptable salts thereof for use in the treatment of migraine.

25. Tropyl-3,5-dimethoxybenzoate or a pharmaceutically acceptable salt thereof for use in the treatment of migraine.

26. Tropyl-3-methylbenzoate or a pharmaceutically acceptable salt thereof for use in the treatment of migraine.

27. Tropyl-3,5-dimethylbenzoate or a pharmaceutically acceptable salt thereof for use in the treatment of migraine.

28. Tropyl-3,4,5-trimethylbenzoate or a pharmaceutically acceptable salt thereof for use in the treatment of migraine.

29. Tropyl-3,4,5-trichlorobenzoate and pharmaceutically acceptable salts thereof for use in the treatment of migraine.

30. A method as claimed in Claim 22 substantially as hereinbefore described.

31. A compound as claimed in Claim 16 whenever prepared by a method as claimed in any one of Claims 36, 37 and 44.

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